Ambulatory and conventional pulse pressures and mean pressures as determinants of the Sokolow-Lyon ECG voltage index in older patients with systolic hypertension

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Introduction

M-mode echocardiography is considered the gold standard for measuring left ventricular mass [1]. However, this technique is difficult to implement in large multicentre studies because obese and older patients or subjects with pulmonary disorders are often not echogenic, leading to their exclusion [2] and possible bias in the study sample. By contrast, a standard 12-lead ECG can easily be obtained in all subjects. Moreover, several studies have shown that precordial voltages are significantly correlated with echo-determined left ventricular mass. In addition, the sensitivity of ECG detection of left ventricular hypertrophy has been demonstrated to increase with age and may be greater in a population with greater pathological extremes of left ventricular hypertrophy [3].

Observational studies [4–9] and recent overviews, [10,11] all based on the calculation of pulse pressure and mean pressure from conventional blood pressure readings, suggested that in middle-aged and older subjects cardiovascular prognosis gets worse with higher pulse pressure, not mean pressure. Until now, no study addressed the question whether the use of ambulatory pulse pressure or ambulatory mean pressure may further enhance the risk stratification of hypertensive patients.

In this article, we used the baseline ambulatory blood pressure recordings obtained in the Systolic Hypertension in Europe (Syst-Eur) trial [12] to investigate whether ambulatory pulse pressure correlates with the Sokolow-Lyon voltage index independent of the ambulatory mean pressure and independent of the pulse pressure calculated from conventional blood pressure readings.

Methods

The protocol of the Syst-Eur trial, described elsewhere [13], was approved by the ethics committees of all participating centres. Eligible patients had to be at least 60 years old, and to have when seated a systolic pressure of 160–219 mmHg with diastolic pressure below 95 mmHg. These blood pressure criteria rested on the mean of six conventional readings obtained in the sitting position during the placebo run-in period (two readings at three visits one month apart). The present paper only includes baseline data.

Forty-six of 198 Syst-Eur centres opted to enrol their

patients in the side project on ambulatory measurement [14]. Validated [15] monitors were programmed to obtain measurements at intervals no longer than 30 minutes. The cuff was secured to the non-dominant arm except if on conventional sphygmomanometry, the difference in systolic pressure between both arms was 10 mm Hg or more, in which case the arm giving the highest reading was chosen for all blood pressure measurements. If arm circumference exceeded 31 cm, cuffs with 35×15 cm bladder were used.

Of 837 randomised patients with a 24 h recording at entry, 29 (3.5%) were excluded because more than 20% of the required readings were unavailable. The remaining 808 patients had their baseline recording before randomisation (n = 695) or shortly (median 4 months, interquartile range 2-5 months) after randomisation (n = 113). From unedited recordings we computed time-weighted blood pressure means for the whole day, daytime (from 10 a.m. to 8 p.m.) and night time (from midnight to 6 a.m.) [14]. Pulse pressure was defined as systolic minus diastolic blood pressure. Ambulatory mean pressure was measured oscillometrically in 668 patients (82.7%). For ambulatory measurements recorded by an auscultatory monitor and for all conventional blood pressure readings, mean pressure was computed as diastolic pressure plus one third of pulse pressure.

A standard 12-lead ECG was obtained following the procedures specified in the Minnesota Code for the standardization of ECG recordings [16]. The voltages of the R-wave in lead V_5 (RV_5) and the S-wave in lead V_1 (SV_1) were measured by the local investigator and checked against the original ECG recording at the Coordinating Office. The Sokolow-Lyon voltage index was calculated as the sum of SV_1 and RV_5 [17].

We based our statistical analysis on two-sided tests, using SAS software version 8.01 (Cary, North Carolina, USA). Means were compared by the standard normal z-test and proportions by the χ^2 statistic. We used single and multiple linear repression analysis to study the correlates of pulse pressure and the Sokolow-Lyon voltage index. The independent effects of the conventional and ambulatory pulse and mean arterial pressures on left ventricular size was assessed using multiple linear and logistic regression analysis.

Results

Patients characteristics

The characteristics of the 311 men and 497 women included in the present analysis were similar to those of the total study population (Table 1). Median age was 69 years (range 60–93). Previous cardiovascular complications were present in 215 patients, of whom 119 had a Sokolow-Lyon voltage index [17] compatible with left ventricular hypertrophy.

Systolic, diastolic, pulse and mean pressures (Table 2) were similar in men and women. Pulse pressure measured in the clinic was on average 19.9 mmHg higher

Table 1 **Patient characteristics and ECG voltages**

	Men	Women	Both sexes
Number of patients	311	497	808
Characteristics			
Age, years	69.4 ± 6.1	69.8 ± 6.3	69.6 ± 6.2
Body-mass index, kg/m^2	26.1 ± 3.2	27.0 ± 4.4***	26.7 ± 4.0
Conventional heart rate, beats/min	72.4 ± 9.6	74.1 ± 8.6*	73.5 ± 9.0
Previous antihypertensive medication, *n* (%)	108 (34.7%)	236 (47.5%)***	344 (42.6%)
Cardiovascular complications, *n* (%)	111 (35.7%)	104 (20.9%)***	215 (26.6%)
Current smokers, *n* (%)	46 (14.8%)	23 (4.6%)***	69 (8.5%)
≥ 1 unit alcohol per day, *n* (%)	82 (26.4%)	42 (8.5%)***	124 (15.3%)
ECG voltages, mV			
SV_1	1.01 ± 0.54	1.02 ± 0.48	1.02 ± 0.50
RV_5	1.74 ± 0.68	1.46 ± 0.55***	1.57 ± 0.62
Sokolow-Lyon voltage index	2.75 ± 0.97	2.49 ± 0.80***	2.59 ± 0.88

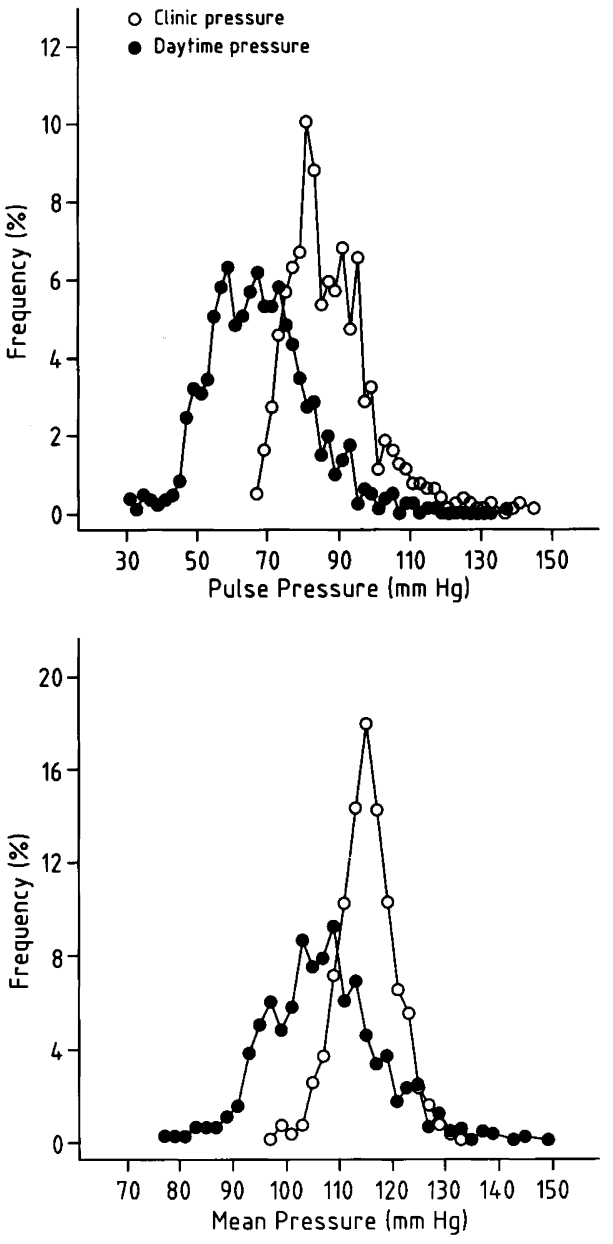
SV_1, S-wave voltage in lead V_1; RV_5, R-wave voltage in lead V_5.
*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$ for the comparison between men and women.
Values are means ± SD or number of subjects (%).

Table 2 **Untreated blood pressure in 808 patients**

Technique of measurement	Mean (SD) values of blood pressure (mmHg)			
	Systolic pressure	Diastolic pressure	Pulse pressure	Mean pressure
Conventional sphygmomanometry*	173.3 (10.8)	86.0 (5.8)	87.3 (12.1)	115.2 (5.5)
Ambulatory monitoring				
24 h	145.8 (15.6)	79.3 (8.9)	66.5 (13.3)	102.3 (10.1)
Daytime (from 10 a.m. to 8 p.m.)	151.4 (16.2)	84.1 (9.8)	67.3 (13.9)	107.1 (10.7)
Night time (from midnight to 6 a.m.)	134.0 (18.6)	70.2 (10.1)	63.8 (14.7)	92.2 (11.9)

*Mean of six readings, i.e. two readings obtained at each of three run-in visits.

Fig. 1



Distribution of the conventional and ambulatory pulse pressures (top panel) and mean pressures (bottom panel).

($p < 0.001$) than the daytime ambulatory pulse pressure (Figure 1). Similarly, mean pressure was on average 8.0 mmHg higher on conventional than on daytime ambulatory measurement (Figure 1).

Correlates of pulse pressure

In both men and women, the conventional, 24 h, daytime and night time pulse pressures tended to increase with age. The Pearson correlation coefficients ($p < 0.001$) in the two sexes combined were 0.23, 0.24, 0.16, and 0.28, respectively. Pulse pressure was not related to body mass index.

Correlates of Sokolow-Lyon voltage index

The Sokolow-Lyon voltage index was 0.26 mV ($p < 0.001$) higher in men than in women (Table 1) and decreased with age (Pearson $r = -0.08$, $p = 0.02$) and body-mass index ($r = -0.18$, $p < 0.001$). By contrast, the Sokolow-Lyon voltage index was similar in patients who had been treated with antihypertensive drugs before enrolment and those who were not receiving antihypertensive medication (2.58 ± 0.90 *vs* 2.59 ± 0.87, $p = 0.89$). In multiple regression analysis the Sokolow-Lyon index was 0.21 mV ($p < 0.001$) higher in men than in women, decreased by 0.14 mV ($p = 0.004$) per decade and by 0.04 mV ($p < 0.001$) per kg/m^2 increase in body-mass index.

Blood pressure as determinant of the Sokolow-Lyon voltage index

Using multiple linear regression analysis, accounting for sex, age and body-mass index, the Sokolow-Lyon voltage index was related to blood pressure. The regression coefficients for systolic pressure were also adjusted for diastolic pressure and vice versa. Similarly, the regression coefficients for pulse pressures and mean pressures were mutually adjusted. Conventional and ambulatory systolic pressures, pulse pressures and mean pressures were significantly and positively related to the Sokolow-Lyon index, whereas the regression coefficient for the night time diastolic pressure was negative (Table 3). For a fixed level of 24 h mean pressure, a 10 mmHg increase in 24 h pulse pressure was associated with a 0.12 mV ($p < 0.001$) higher Sokolow-Lyon index. Furthermore, after additional adjustment for the conventional pulse pressure, the regression coefficient for the 24 h pulse pressure remained statistically significant (0.12, $p < 0.001$).

Using multiple logistic regression analysis, accounting for the same covariables, the odds of having a Sokolow-Lyon index compatible with left ventricular hypertrophy (≥ 3.5 mV) was correlated with blood pressure. The adjusted odds ratios were significant for all types of systolic pressure and pulse pressure and for the conventional and 24 h mean pressures (Table 3). For a fixed level of the 24 h mean pressure, a 10 mmHg increase in the 24 h pulse pressure increased the odds by 24% ($p = 0.01$). Furthermore, after additional adjustment for the conventional pulse pressure, the odds ratio of the 24 h pulse pressure remained significant (1.21, $p = 0.048$).

In both the linear and logistic regression models, the slope of the relationship between the conventional and

Table 3 **Blood pressure as a determinant of the Sokolow-Lyon voltage index [17]**

	Systolic pressure	Diastolic pressure	Pulse pressure	Mean pressure
Linear regression coefficient				
Conventional	0.18 (0.13,0.24)***	− 0.03 (− 0.08,0.03)	0.14 (0.08,0.19)***	0.12 (0.01,0.23)*
24 h	0.16 (0.12,0.21)***	− 0.03 (− 0.07,0.01)	0.12 (0.08,0.17)***	0.12 (0.05,0.18)***
Daytime	0.13 (0.08,0.17)***	− 0.02 (− 0.06,0.01)	0.10 (0.05,0.14)***	0.09 (0.03,0.15)**
Night time	0.16 (0.12,0.20)***	− 0.06 (− 0.10,− 0.02)**	0.14 (0.09,0.19)***	0.06 (0.00,0.11)*
Odds ratio for Sokolow-Lyon index ≥ 3.5 mV [17]				
Conventional	1.50 (1.27,1.78)***	1.01 (0.85,1.20)	1.30 (1.10,1.53)**	1.48 (1.01,2.17)*
24 h	1.35 (1.16,1.58)***	0.96 (0.83,1.10)	1.24 (1.05,1.47)*	1.31 (1.05,1.63)*
Daytime	1.28 (1.11,1.47)***	0.94 (0.83,1.07)	1.21 (1.04,1.41)*	1.19 (0.97,1.46)
Night time	1.35 (1.17,1.57)***	0.91 (0.80,1.04)	1.29 (1.10,1.52)**	1.16 (0.96,1.41)

*Regression coefficients and odds ratios were calculated for 10 mmHg increases in systolic, mean or pulse pressures, or 5 mmHg increase in diastolic pressure. All estimates were adjusted for sex, age and body-mass index. In addition, mutual adjustments were applied for systolic and diastolic pressures and for pulse and mean pressures.
Significance levels are indicated: $^{*}p \leq 0.05$, $^{**}p < 0.01$ and $^{***}p < 0.001$.

ambulatory pulse pressure and the Sokolow-Lyon index was not different between patients who had been treated with antihypertensive drugs before enrolment and those who were not receiving antihypertensive medication in the six months preceding the placebo run-in period.

Discussion

Cross-sectional analysis of the ECG data obtained at entry in the Syst-Eur trial produced three major findings. First, electrocardiographic left ventricular mass as assessed by the Sokolow-Lyon index is better correlated with systolic than with diastolic blood pressure. Second, pulse pressure and mean pressure are independent determinants of electrocardiographic left ventricular mass in this population. Third, ambulatory blood pressure monitoring adds to the diagnostic precision of the conventional blood pressure in evaluating the severity of hypertension. Indeed, the Sokolow-Lyon index was significantly correlated with ambulatory measurements of blood pressure over and beyond the corresponding conventional clinic measurements.

The finding that systolic blood pressure was a stronger correlate of the Sokolow-Lyon voltage index than diastolic blood pressure in this elderly population is consistent with the observations of Franklin *et al*., who showed that, with advancing age, there was a shift from diastolic pressure to systolic pressure as predictors of coronary heart disease risk in the Framingham Heart Study [18]. In 7757 older patients (≥ 60 years) with isolated systolic hypertension who had been randomized to the control groups of eight intervention trials, total mortality was positively correlated with systolic pressure at entry, whereas the association with diastolic pressure was negative [11]. Not only the age of the patients, but also the selection of the subjects on the basis of a high systolic (≥ 160 mmHg) and a low diastolic (< 95 mmHg) blood pressure probably contributed to the observed closer relationship between electrocardiographic left ventricular mass and systolic as opposed to diastolic pressure.

Current guidelines for the diagnosis and management of hypertension rest almost completely on systolic and diastolic blood pressure, two specific inflection points of the blood pressure wave [19]. However, in 1989 Darne *et al*., [4] suggested that the blood pressure wave may be more accurately described as consisting of a steady component, mean pressure, and a pulsatile component, pulse pressure. Our finding that pulse pressure and mean pressure were independently related to the Sokolow-Lyon voltage index is in agreement with other cross-sectional studies. The Atherosclerosis Risk in Communities study showed that, after adjustment for age and body weight, electrocardiographic left ventricular mass was positively and independently correlated with greater pulse pressure and higher mean pressure [20]. In 27,687 French adults aged 40 to 69 years, both the steady and pulsatile components of blood pressure were higher in subjects with electrocardiographic evidence of left ventricular hyperthrophy than in those without hyperthrophy [4]. A case-control study of coronary heart disease showed that increased left ventricular mass was positively associated with proximal aortic stiffness [21]. In 79 normotensive subjects and 197 otherwise healthy hypertensive patients, the extent to which arterial stiffness related to echocardiographic left ventricular mass was dependent on the method by which arterial stiffness had been estimated [22]. Pressure-dependent methods showed an association with left ventricular hypertrophy, whereas the pressure-independent stiffness index (β) and the arterial compliance index were most strongly associated with aging and left ventricular remodelling, but not hypertrophy [22].

The finding that ECG left ventricular size was significantly related to the ambulatory pulse pressure over and beyond conventional pulse pressure is in line with our previous findings that ambulatory monitoring compared to conventional blood pressure measurement, enhances the risk stratification of older patients with isolated systolic hypertension [14,23,24]. These observations are also consistent with the findings of Verdecchia *et al*.,

[25] who showed that cardiovascular morbidity in 2010 initially untreated subjects with uncomplicated essential hypertension was more closely predicted by ambulatory than by office pulse pressure even after controlling for multiple risk factors. The greater number of measurements, the absence of digit preference and observer bias, and the minimization of the white-coat effect probably contributed to these observations. In addition, the measurement technique could have played a role. Indeed the ambulatory mean pressure was directly measured by an oscillometric technique in the majority of the patients whereas the conventional mean pressure was always calculated from auscultatory blood pressure readings.

In conclusion, in older hypertensive patients pulse pressure and mean pressure are independent determinants of the Sokolow-Lyon voltage index. In addition 24 h ambulatory pulse pressure adds to the diagnostic precision of the conventional pulse pressure in assessing the severity of hypertension in relation to electrocardiographic left ventricular mass.

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